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Factors that predict in-hospital mortality in eosinophilic granulomatosis with polyangiitis

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Abstract

Background: Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic small-vessel vasculitis associated with asthma, eosinophilia, and necrotizing vasculitis. EGPA is potentially life-threatening and often involves peripheral neuropathies, peptic ulcers, cerebral vessel disease, and cardiovascular disease. However, there is limited understanding of the prognostic factors for patients with EGPA. We investigated the clinical features and factors affecting patients' in-hospital mortality, using a national inpatient database in Japan.

Methods: We retrospectively collected data for EGPA patients who required hospitalization between July 2010 and March 2013, using the Diagnosis Procedure Combination database. We evaluated EGPA patients' characteristics and performed multivariate logistic regression analyses to assess the factors associated with in-hospital mortality.

Results: A total of 2195 EGPA patients were identified. The mean age was 61.9 years, 42.1% (924/2195) were male, and 41.6% (914/2195) had emergent admission. In-hospital deaths occurred in 97/2195 patients (4.4%). Higher in-hospital mortality was associated with age older than 65 years, disturbance of consciousness on admission, unscheduled admission, respiratory disease, cardio-cerebrovascular disease, renal disease, sepsis, and malignant disease on admission. Lower mortality was associated with female gender and peripheral neuropathies.

Conclusions: Our study revealed the clinical features of EGPA patients who required hospitalization and the factors associated with their mortality. These results may be useful for physicians when assessing disease severity or treatments for hospitalized EGPA patients.

Keywords eosinophilic granulomatosis with polyangiitis; peripheral neuropathy; predictive factors for in-hospital mortality

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA, previously called Churg-Strauss syndrome) is a rare systemic small-vessel vasculitis that occasionally develops in patients with asthma. EGPA is characterized by eosinophilia, eosinophilic infiltration of various tissues, and necrotizing vasculitis (1-3). EGPA can affect virtually any organ system and causes pulmonary infiltration, allergic rhinitis, peripheral neuropathy, and can involve the central nervous system, gastrointestinal system, heart, skin, and kidneys (2, 4, 5).

Several previous studies on EGPA patients identified the factors associated with long-term mortality (6–8), including proteinuria, renal insufficiency, central nervous system involvement, cardiomyopathy, severe gastrointestinal involvement, age older than 65 years, and lack of ear nose and throat (ENT) symptoms, known as the five-factor score (FFS) and the new FFS (7, 8). Patients with EGPA who require hospitalization are considered to have a higher risk of death; however, there is limited understanding of the factors associated with in-hospital mortality in these patients. To our knowledge, there are no large-scale studies describing the clinical characteristics and mortality in hospitalized EGPA patients.

We aimed to investigate the clinical features and in-hospital mortality of EGPA patients who required hospitalization and to verify patients' conditions and comorbidities at admission that affect in-hospital mortality.

Methods

Diagnosis Procedure Combination (DPC) database

We examined data abstracted from the Japanese DPC database, which is a nationwide inpatient database in Japan. The database includes administrative claims data and discharge abstract data. Types of hospital, main diagnoses, comorbidities on admission, and complications occurring during hospitalization that were diagnosed and recorded by attending physicians, are indicated using the International Classification of Disease and Related Health Problems, 10th Revision (ICD-10) codes accompanied by text data in Japanese. The database also contains the following patient details: admission status; age; sex; body height and weight; levels of consciousness based on the Japan Coma Scale (9, 10) on admission and discharge; discharge status including in-hospital death; and medication use during hospitalization.

This study was approved by the Institutional Review Board of The University of Tokyo, which waived the requirement for patient informed consent because of the anonymous nature of the data.

Patient selection and data

We retrospectively collected data for patients with a diagnosis of EGPA (ICD-10 code, M301) as the main diagnosis or comorbidity, who were discharged between 1 July 2010 and 31 March 2013.

Although the diagnosis of EGPA is generally made by specialists based on the American College of Rheumatology criteria (11), the accuracy of the recorded diagnoses in the database was not validated in all patients.

The following comorbidities on admission were identified using ICD-10 codes and text data in Japanese: pneumonia (bacterial pneumonia: J13-15, J170; atypical pneumonia: A481, J157, J160; aspiration pneumonia: J69; pneumocystis pneumonia: B59; eosinophilic pneumonia: J82; interstitial pneumonia: J841, J848-9); alveolar hemorrhage: R048; cardiovascular disease (heart failure: I50; myocardial infarction: I21-23; angina pectoris: I20; pericarditis: B332, I30-32; myocarditis: B332,

I40–41, I514; valvular disease: I36–39; arrhythmia: I44–49; cardiomyopathy: I42–43); cerebrovascular disease (cerebral infarction, I63, I693; cerebral hemorrhage: I60–62, I690–692; transient ischemic attack: G45); peripheral neuropathy: G629, G64; digestive disease (liver disease: K70–77; gastrointestinal bleeding: K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K286, K920, K922; gastrointestinal perforation: K223, K251, K252, K255, K256, K261, K262, K265, K266, K271, K272, K275, K276, K281, K282, K285, K286, K570, K572, K574, K578, K631; ileus: K56; acute pancreatitis: K85); renal disease (glomerular disease: N00–08; renal tubule-interstitial disease: N10–16; acute kidney failure and chronic kidney disease: N17–19); sepsis: A021, 207, 227, 267, 327, A40, A41, 427, B377); malignant disease (including types of malignancy): C00–97; and ear nose throat (ENT) disease: (H60–95, J00–06, J30–39). Pneumonia, interstitial pneumonia, and alveolar hemorrhage were combined under the heading, “pulmonary disease”, and cardiovascular diseases and cerebrovascular disease were combined under the heading, “cardio-cerebrovascular diseases”.

To evaluate the effect of in-hospital mortality on disease severity, we assessed EGPA patients using a scoring system based on the FFS, using data from patients’ conditions on admission, as follows; age > 65 years: +1 point, presence of cardiac disease: +1 point, gastrointestinal involvement: +1 point, renal disease: +1 point, and absence of ear, nose, and throat (ENT) symptoms: +1 point. We then divided these patients into three groups scoring the severity of disease as ‘mild’ (score 0), ‘moderate’ (score 1), and ‘severe’ (score ≥ 2).

We also collected data on immunomodulatory medications, such as intravenous immunoglobulin therapy, immunosuppressive drugs (azathioprine, cyclosporine, mizoribine, tacrolimus hydrate, methotrexate, and cyclophosphamide), and steroid pulse therapy (methylprednisolone ≥ 500 mg/day administered more than once per day), which were begun within two days after admission to evaluate the effects of early intervention with immunomodulatory

treatments on in-hospital mortality. We also recorded the use of these immunomodulatory drugs during hospitalization.

Statistical analysis

Chi-square tests were used to compare proportions among the groups; Kruskal-Wallis tests were used to compare the median values among the groups; and multivariable logistic regression for in-hospital mortality was performed to analyze factors associated with in-hospital mortality. When performing the multivariable logistic regression, two patients with missing admission status data were excluded. The threshold for significance was a P -value < 0.05 . All statistical analyses were performed using SPSS version 22.0 (IBM SPSS Inc., Armonk, NY, USA).

Results

Patient characteristics and admission status

Among 19 million patients recorded during 33 months between July 2010 and March 2013, we identified 2195 patients with a diagnosis of EGPA. The mean age was 61.9 years (standard deviation [SD], 15.6), and 51.0% (1120/2195) were under 64 years of age. Overall, 924 patients (42.1%) were male and the mean body mass index was 21.4 (SD, 4.0). There were 96 patients (4.4%) whose consciousness level was not alert and approximately 40% (914/2195) of patients had unscheduled admission. The median length of stay was 23 days (interquartile range, 9–49 days) and the proportion of patients in academic hospitals was 41.3% (906/2195). Regarding the comorbidities on admission, the prevalence of pulmonary disease was 12.8%; cardio-cerebrovascular disease, 17.1%; peripheral neuropathy, 19.6%; digestive disease, 5.1%; renal disease, 7.2%; sepsis, 1.4%; and malignant disease, 5.8%. The types of malignancies were 21 (16.5%) carcinomas of the colon and

rectum, 18 (14.2%) lung cancers, 10 (7.9%) leukemias, 10 (7.9%) prostatic cancers, nine (7.1%) gastric cancers, nine (7.1%) malignant lymphomas, eight (6.3%) hepatocellular carcinomas, six (4.7%) breast cancers, five (4.0%) gallbladder and bile duct cancers, four (3.1%) bladder cancers, and 27 (21.3%) other cancers.

All-cause in-hospital mortality

Among 2195 patients, there were 97 in-hospital deaths (4.4%). In-hospital mortality rates for the severity scores, 'mild', 'moderate', and 'severe' were 0%, 1.2%, and 7.0%, respectively ($P < 0.001$). The median length of stay in patients who died during hospitalization was 37 days (interquartile range, 15–60 days), which was significantly longer than that of surviving patients (median, 22 days; interquartile range, 9–48 days; $P = 0.008$). Table 1 shows the relationship between in-hospital mortality and patient's characteristics, admission status, medication within two days after admission, and comorbidities on admission. In-hospital mortality was related to age older than 65 years ($P < 0.001$), male gender ($P = 0.001$), disturbance of consciousness on admission ($P < 0.001$), unscheduled admission ($P < 0.001$), steroid pulse therapy during hospitalization ($P < 0.001$), and the following comorbidities on admission: pulmonary disease ($P < 0.001$); cardio-cerebrovascular disease ($P < 0.001$); peripheral neuropathy ($P < 0.001$); renal disease ($P = 0.001$); sepsis ($P < 0.001$); and malignant disease ($P = 0.001$). BMI; type of hospital; immunoglobulin, immunosuppressive drugs, and steroid pulse therapy begun within two days after admission; immunoglobulin, and immunosuppressive drugs during hospitalization; and digestive disease were not significant factors associated with in-hospital death.

Compared with patients without peripheral neuropathy, those with peripheral neuropathy were prescribed significantly more immunoglobulin (7.1% vs. 16.0%, $P < 0.001$), and steroid pulse therapy (8.8% vs. 16.5%, $P < 0.001$) within two days after admission.

Multivariable logistic regression for all-cause in-hospital mortality

Because no EGPA patients with ENT diseases ($n = 130$) died during hospitalization in this study period, we excluded the ENT diseases from the independent variables in the logistic regression for in-hospital mortality. Table 2 shows the results of the multivariable logistic regression analysis for all-cause in-hospital mortality. Higher mortality in the EGPA patients was associated with age > 65 years (odds ratio, 2.39 [95% confidence interval, 1.41–4.05]); disturbance of consciousness on admission (3.94 [2.20–7.07]); unscheduled admission (2.27 [1.39–3.70]); respiratory disease (2.60 [1.60–4.21]); cardio-cerebrovascular disease (1.67 [1.03–2.70]); renal disease (2.24 [1.21–4.17]); sepsis (3.33 [1.30–8.56]); and malignant disease (2.59 [1.33–5.02]) on admission. Lower mortality was associated with female gender (0.61 [0.39–0.95]) and the presence of peripheral neuropathy (0.32 [0.12–0.90]) on admission.

Discussion

Our analysis revealed the clinical characteristics, admission status, and all-cause in-hospital mortality in patients with EGPA who required hospitalization, using a national inpatient database in Japan.

Several recent reports have shown relatively favorable five-year survival rate (90–97%) of EGPA patients (12, 13). However, to our knowledge, there has been no study reporting the short-term mortality of hospitalized EGPA patients. The mean age on admission in this study was 61.9 years (SD, 15.6), which was higher than for patients 40–50 years of age at onset reported in previous studies (4, 7, 12–19). The male to female ratio in our study was approximately 1:1.4; therefore, the female predominance was similar to a previous study in Japan (15), although the majority of previous studies from Western countries showed no difference in the proportion of male vs. female patients with EGPA (4, 5, 14, 17, 20). The male to female ratio in the general population in Japan is 1:1.05, and similar to that of 1:1.04 in the UK and 1:1.03 in the US population (21); therefore, the female

predominance in EGPA patients in Japan contributes to the genetic influence on the pathogenesis of EGPA.

In the present study, we reported the types of malignancy seen in EGPA patients, but it was difficult to determine if the malignant diseases had a relationship to EGPA or prior EGPA therapy because data on time of diagnosis or prior therapy were not included in the DPC database.

In previous studies of patients with antineutrophil cytoplasmic antibody-associated vasculitides (AAV), proteinuria, renal insufficiency, central nervous system involvement, cardiomyopathy, severe gastrointestinal involvement (bleeding, perforation, infarction, and/or pancreatitis), and age older than 65 years were significantly associated with higher 5-year mortality (6, 12-14, 22). In our study, the higher in-hospital mortality was associated with age older than 65 years, cardio-cerebrovascular disease and renal disease. Male gender, disturbance of consciousness, requirement for emergency admission, respiratory disease, sepsis, and malignant disease on admission were also associated with higher mortality.

The presence of ENT symptoms has been reported to be associated with lower relative risk of long-term mortality (8). In our study, there was no death in 130 EGPA patients with ENT diseases. These findings suggest that the presence of ENT diseases is associated with lower mortality in EGPA patients.

Gastrointestinal (GI) manifestations were seen in approximately 10–20% of EGPA patients in previous reports (12, 13, 23). Symptoms were mainly abdominal pain, nausea, vomiting, or diarrhea (12, 13, 23), and severe GI involvement was rare (13). One study stated that severe GI involvement was seen in 20–50% of the patients with GI involvement (23) and another study found that only 1.8% of all patients with AAV had severe GI manifestation, defined as a risk factor in FFS (13). Contrary to previous studies of patients with AAV, the presence of severe digestive disease on

admission was not significantly associated with higher mortality in this study, possibly because severe GI involvement was rare.

Peripheral neuropathy is a major complication in EGPA, present in approximately 70% of patients with EGPA (24), and its impact on function and quality of life is a serious problem. However, one study reported that causes of death in patients with peripheral neuropathy were diffuse alveolar hemorrhage, infection, acute renal failure, and gastrointestinal perforation, and that no patients died directly of neuropathy (25). A previous study also reported that the presence of peripheral neuropathy was not associated with mortality (26). We found that the presence of peripheral neuropathy was significantly associated with lower mortality. Early intensive medical treatment, including intravenous immunoglobulin (IVIG), and steroid pulse therapy may be related to favourable outcomes in EGPA patients with peripheral neuropathy.

Corticosteroid treatment for EGPA is generally recommended, consisting of tapered high dose steroids (27-29). However, in cases of severe disease or corticosteroid resistance, cyclophosphamide should be considered as an additional therapy (3, 27-30). Steroid pulse therapy, IVIG, and immunosuppressive agents should be administered to EGPA patients with severe complications or fulminant disease (27, 30, 31). Therefore, we evaluated the relationship between in-hospital mortality and IVIG, immunosuppressive drugs, and steroid pulse therapy begun within two days after admission, which were used to achieve remission. Our study did not demonstrate that early introduction of treatment for EGPA was associated with lower mortality. Once remission inductive therapy is begun, based on patients' disease severity, more than 90% of patients achieve first remission, although relapse occurs in 25–40% of patients, regardless of their initial disease severity (6, 13, 32). In a previous study, approximately 90% of relapsed patients achieved new remission, and relapse did not impact overall survival (6). In our study, early intervention was not associated with prognosis, possibly because the results of remission induction treatment are generally favorable (6).

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There was also a significant relationship between steroid pulse therapy during hospitalization and in-hospital mortality, possibly because patients requiring steroid pulse therapy suffered more severe physical symptoms.

Our study has certain limitations, one of which was the accuracy of the EGPA diagnosis. Because this study was a retrospective investigation based on information from an administrative database, in which all data were de-identified, we were unable to confirm whether each patient satisfied the diagnostic criteria (11). However, because patients who are suspected of having EGPA are usually referred to rheumatologists or respiratory physicians in Japan, it is expected that the diagnosis of EGPA is generally performed and validated by the specialists.

In conclusion, all-cause in-hospital mortality was associated with age older than 65 years, male gender, disturbance of consciousness on admission, unscheduled admission, and the presence of respiratory disease, cardio-cerebrovascular disease, renal disease, sepsis, and malignant disease on admission. Conversely, lower mortality was associated with the presence of peripheral neuropathy on admission, which may be related to intensive EGPA treatment. Also, the presence of ENT disease was associated with lower mortality in EGPA patients. To our knowledge, this is the first study examining in-hospital mortality using the factors recorded on admission, and our findings should help physicians when considering disease severity or medical treatment for patients with EGPA.

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Author contributions: WH: study design, data analysis, data interpretation, and manuscript preparation; YY: study design, data analysis, data interpretation, and manuscript preparation; HY: study design, data collection, data analysis, data interpretation, and manuscript preparation; MS: study design and data interpretation; TJ: study design and data interpretation; HM: study design, data collection, data analysis, and data interpretation; KF: data collection and data interpretation; KT: study design and data interpretation; TN: study design, data interpretation, and supervision of the study. All authors approved the final manuscript.

Conflict of Interest Statement

All of the authors declare that they have no conflicts of interest to disclose.

References

1. Churg J, Strauss L. Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. *Am J Pathol* 1951;**27**:277-301.
2. Noth I, Streck ME, Leff AR. Churg-Strauss syndrome. *Lancet* 2003;**361**:587-94.
3. Szczeklik W, Jakiela B, Adamek D, Musial J. Cutting edge issues in the Churg-Strauss syndrome. *Clin Rev Allergy Immunol* 2013;**44**:39-50.
4. Conron M, Beynon HL. Churg-Strauss syndrome. *Thorax* 2000;**55**:870-877.
5. Katzenstein AL. Diagnostic features and differential diagnosis of Churg-Strauss syndrome in the lung. A review. *Am J Clin Pathol* 2000;**114**:767-772.
6. Samson M, Puechal X, Devilliers H, Ribi C, Cohen P, Stern M, et al. Long-term outcomes of 118 patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) enrolled in two prospective trials. *J Autoimmun* 2013;**43**:60-69.
7. Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, et al.

Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. *Medicine* 1996;**75**:17-28.

8. Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P, et al. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. *Medicine* 2011;**90**:19-27.

9. Ohta T, Waga S, Handa W, Saito I, Takeuchi K. [New grading of level of disordered consciousness (author's transl)]. *No Shinkei Geka* 1974;**2**:623-627.

10. Todo T, Usui M, Takakura K. Treatment of severe intraventricular hemorrhage by intraventricular infusion of urokinase. *J Neurosurg* 1991;**74**:81-86.

11. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum* 1990;**33**:1094-1100.

12. Moosig F, Bremer JP, Hellmich B, Holle JU, Holl-Ulrich K, Laudien M, et al. A vasculitis centre based management strategy leads to improved outcome in eosinophilic granulomatosis and polyangiitis (Churg-Strauss, EGPA): monocentric experiences in 150 patients. *Ann Rheum Dis* 2013;**72**:1011-1017.

13. Comarmond C, Pagnoux C, Khellaf M, Cordier JF, Hamidou M, Viallard JF, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. *Arthritis Rheum* 2013;**65**:270-281.

14. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine* 1999;**78**:26-37.

15. Sada KE, Amano K, Uehara R, Yamamura M, Arimura Y, Nakamura Y, et al. A nationwide survey on the epidemiology and clinical features of eosinophilic granulomatosis with polyangiitis (Churg-Strauss) in Japan. *Mod Rheumatol* 2014;**24**:640-644.

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16. Gayraud M, Guillevin L, le Toumelin P, Cohen P, Lhote F, Casassus P, et al. Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. *Arthritis Rheum* 2001;**44**:666-675.
 17. Keogh KA, Specks U. Churg-Strauss syndrome: clinical presentation, antineutrophil cytoplasmic antibodies, and leukotriene receptor antagonists. *Am J Med* 2003;**115**:284-290.
 18. Sable-Fourtassou R, Cohen P, Mahr A, Pagnoux C, Mouthon L, Jayne D, et al. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. *Ann Intern Med* 2005;**143**:632-638.
 19. Abril A. Churg-strauss syndrome: an update. *Curr Rheumatol Rep* 2011;**13**:489-495.
 20. Pagnoux C, Guilpain P, Guillevin L. Churg-Strauss syndrome. *Curr Opin Rheumatol* 2007;**19**:25-32.
 21. United Nations. population and vital statistics report 2014. Available from URL: http://unstats.un.org/unsd/demographic/products/vitstats/Sets/Series_A_2014.pdf.
 22. Bourgarit A, Le Toumelin P, Pagnoux C, Cohen P, Mahr A, Le Guern V, et al. Deaths occurring during the first year after treatment onset for polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: a retrospective analysis of causes and factors predictive of mortality based on 595 patients. *Medicine* 2005;**84**:323-330.
 23. Pagnoux C, Mahr A, Cohen P, Guillevin L. Presentation and outcome of gastrointestinal involvement in systemic necrotizing vasculitides: analysis of 62 patients with polyarteritis nodosa, microscopic polyangiitis, Wegener granulomatosis, Churg-Strauss syndrome, or rheumatoid arthritis-associated vasculitis. *Medicine* 2005;**84**:115-128.
 24. Vaglio A, Buzio C, Zwerina J. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): state of the art. *Allergy* 2013;**68**:261-273.
 25. Zhang W, Zhou G, Shi Q, Zhang X, Zeng XF, Zhang FC. Clinical analysis of nervous system involvement in ANCA-associated systemic vasculitides. *Clin Exper Rheumatol*

2009;**27**(1 Suppl 52):S65-69.

26. Suppiah R, Hadden RD, Batra R, Arden NK, Collins MP, Guillevin L, et al. Peripheral neuropathy in ANCA-associated vasculitis: outcomes from the European Vasculitis Study Group trials. *Rheumatology* 2011;**50**:2214-2222.
27. Bosch X, Guilabert A, Espinosa G, Mirapeix E. Treatment of antineutrophil cytoplasmic antibody associated vasculitis: a systematic review. *JAMA* 2007;**298**:655-669.
28. Cohen P, Pagnoux C, Mahr A, Arene JP, Mouthon L, Le Guern V, et al. Churg-Strauss syndrome with poor-prognosis factors: A prospective multicenter trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients. *Arthritis Rheum* 2007;**57**:686-93.
29. Ribi C, Cohen P, Pagnoux C, Mahr A, Arene JP, Lauque D, et al. Treatment of Churg-Strauss syndrome without poor-prognosis factors: a multicenter, prospective, randomized, open-label study of seventy-two patients. *Arthritis Rheum* 2008;**58**:586-594.
30. Hellmich B, Gross WL. Recent progress in the pharmacotherapy of Churg-Strauss syndrome. *Expert Opin Pharmacother* 2004;**5**:25-35.
31. Danieli MG, Cappelli M, Malcangi G, Logullo F, Salvi A, Danieli G. Long term effectiveness of intravenous immunoglobulin in Churg-Strauss syndrome. *Ann Rheum Dis* 2004;**63**:1649-1654.
32. Li ZY, Chang DY, Zhao MH, Chen M. Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated vasculitis: a study of 439 cases in a single Chinese center. *Arthritis Rheum* 2014;**66**:1920-1926.

Table 1. All-cause in-hospital mortality in patients with EGPA who required hospitalization

Total (%)	Mortality (%)	P-value
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Age (years)			<0.001
≤64	1120 (51.0)	20 (1.8)	
>65	1075 (49.0)	77 (7.2)	
Sex			0.001
Male	924 (42.1)	56 (6.1)	
Female	1271 (57.9)	41 (3.2)	
BMI (kg/m ²)			0.107
<18.5	448(20.4)	21 (4.7)	
18.5–22.9	961(43.8)	36 (3.7)	
23.0–24.9	285(13.0)	13 (4.6)	
>25.0	318 (14.5)	12 (3.8)	
Missing data	183 (8.3)	15 (8.2)	
Consciousness level			<0.001
Alert	2099 (95.6)	74 (3.5)	
Not alert	96 (4.4)	23 (24.0)	
Admission			<0.001
Scheduled	1279 (58.3)	27 (2.1)	
Unscheduled	914 (41.6)	69 (7.5)	
Missing data	2 (0.1)	1 (50.0)	
Type of hospital			0.057

Academic	906 (41.3)	31 (3.4)	
Non-academic	1289 (58.7)	66 (5.1)	
Immunoglobulin therapy begun within two days after admission			0.094
No	2001 (91.2)	93 (4.6)	
Yes	194 (8.8)	4 (2.1)	
Immunosuppressive drugs begun within two days after admission			0.981
No	2083 (94.9)	92 (4.4)	
Yes	112 (5.1)	5 (4.5)	
Steroid pulse therapy begun within two days after admission			0.729
No	1969 (89.7)	86 (4.4)	
Yes	226 (10.3)	11 (4.9)	
Immunoglobulin therapy during hospitalization			0.910
No	1640(74.7)	72(4.4)	
Yes	555(25.3)	25(4.5)	
Immunosuppressive drugs during hospitalization			0.114
No	1786(81.4)	73(4.1)	
Yes	409(18.6)	24(5.9)	
Steroid pulse therapy during hospitalization			<0.001

No	1682(76.6)	58(3.4)	
Yes	513(23.4)	39(7.6)	
Pulmonary disease			<0.001
No	1914 (87.2)	64 (3.3)	
Yes	281 (12.8)	33 (11.7)	
Pneumonia	211 (9.6)	19 (9.0)	
Interstitial pneumonia	66 (3.0)	14 (21.2)	
Alveolar hemorrhage	17 (0.8)	4 (23.5)	
Cardio-cerebrovascular disease			<0.001
No	1820 (82.9)	65 (3.6)	
Yes	375 (17.1)	32 (8.5)	
Cardiovascular disease	285 (13.0)	27 (9.5)	
Cerebrovascular disease	110 (5.0)	9 (8.2)	
Peripheral neuropathy			<0.001
No	1765 (80.4)	93 (5.3)	
Yes	430 (19.6)	4 (0.9)	
Digestive disease			0.620
No	2083 (94.9)	91 (4.4)	
Yes	112 (5.1)	6 (5.4)	
Renal disease			0.001

No	2036 (92.8)	82 (4.0)	
Yes	159 (7.2)	15 (9.4)	
Sepsis			<0.001
No	2165 (98.6)	89 (4.1)	
Yes	30 (1.4)	8 (26.7)	
Malignant disease			0.001
No	2068 (94.2)	84 (4.1)	
Yes	127 (5.8)	13 (10.2)	

Abbreviations: EGPA = eosinophilic granulomatosis with polyangiitis; BMI = body mass index.

Table 2. Multivariable logistic regression for all-cause in-hospital mortality in EGPA patients

		Odds ratio	95% confidence interval	P-value
Age (years)	≤64	Reference		
	>65	2.39	1.41–4.05	0.001
Sex	Male	Reference		
	Female	0.61	0.39–0.95	0.028
Consciousness level	Alert	Reference		
	Not alert	3.94	2.20–7.07	<0.001
Admission	Scheduled	Reference		
	Unscheduled	2.27	1.39–3.70	0.001
Pulmonary disease	No	Reference		
	Yes	2.60	1.60–4.21	<0.001
Cardio-cerebrovascular disease	No	Reference		
	Yes	1.67	1.03–2.70	0.036
Peripheral neuropathy	No	Reference		
	Yes	0.32	0.12–0.90	0.031
Renal disease	No	Reference		
	Yes	2.24	1.21–4.17	0.011

Sepsis	No	Reference		
	Yes	3.33	1.30–8.56	0.012
Malignant disease	No	Reference		
	Yes	2.59	1.33–5.02	0.005

Abbreviations: EGPA = eosinophilic granulomatosis with polyangiitis.